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09/244,195	02/04/1999	GEORGE BARRIE KITTO	D6073	3475

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EXAMINER	
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Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/244,195	Applicant(s) Kitto, G. And M. Burnett
	Examiner Jeffrey S. Parkin, Ph.D.	Art Unit 1648

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 03 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *18 Sep 2001* .

2a) ☐ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☐ Claim(s) _____ is/are pending in the application.

4a) Of the above, claim(s) _____ is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☐ Claim(s) _____ is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are objected to by the Examiner.

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

15) ☒ Notice of References Cited (PTO-892)

16) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)

17) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____

18) ☐ Interview Summary (PTO-413) Paper No(s). _____

19) ☐ Notice of Informal Patent Application (PTO-152)

20) ☐ Other:

Detailed Office Action

37 C.F.R. § 1.114

1. A request for continued examination under 37 C.F.R. § 1.114, including the fee set forth in 37 C.F.R. § 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 C.F.R. § 1.114, and the fee set forth in 37 C.F.R. § 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 C.F.R. § 1.114.

Status of the Claims

2. Acknowledgement is hereby made of receipt and entry of the submission filed 18 September, 2001, wherein claim 3 was canceled without prejudice or disclaimer and claim 1 amended. Claims 1-2 and 5-11 are pending in the instant application.

35 U.S.C. § 112, Second Paragraph

3. Claims 1, 2, and 5-11 are rejected under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The claims are vague and indefinite since the precise genotypic/phenotypic characteristics of the attenuated bacterial host are not provided. For instance, does the host comprise a plasmid encoding an Lpp-OmpA-X fusion protein? Does the host comprise a plasmid encoding the Lpp-OmpA and X genes at separate loci which results in their individual expression? Or does the host comprise multiple plasmids encoding different proteins (i.e, Lpp-OmpA on plasmid 1 and X on plasmid 2)? Appropriate correction and clarification are required.

35 U.S.C. § 112, First Paragraph

4. The following is a quotation of the first paragraph of 35 U.S.C. § 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 6-10 stand rejected under 35 U.S.C. § 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. Applicants argue that the claims are not drawn toward the generation of anti-HIV immune responses in humans and that the specification is fully enabling for the claimed invention. These arguments are not deemed to be persuasive for the reasons of record previously set forth and as further elaborated below.

Applicants are reminded that the claims are directed toward a method of initiating an immune response specific for HIV-1 in "an individual in need of such treatment". The claims are not specifically directed toward a non-human host, and in fact, encompass the administration of the claimed recombinant bacteria to humans. The disclosure clearly states that the purpose of such an administration is to prevent or treat HIV infection. For instance, on pages 1 and 2 (bridging paragraph) it was disclosed that "The present invention relates to development of a **live vaccine for human immunodeficiency virus (HIV)**." The specification further states (p. 7, second paragraph) that "The present invention discloses development of a model **live vaccine for HIV**, using an attenuated strain of Salmonella engineered to surface express

specific HIV proteins. In one embodiment, there is provided a **live vaccine for human immunodeficiency virus** comprising a recombinant plasmid containing genes required for surface exposure and a gene encoding a human immunodeficiency virus protein." Thus, the focus of the invention as set forth in the specification, is to provide vaccines for the treatment or prevention of HIV infection. Accordingly, the Examiner is assuming that the purpose of the immune response is to generate a protective or therapeutic response in the "individual in need of such treatment". Presumably, this is a human being who is infected with HIV-1 or an individual who is in a high-risk group and would need a vaccine to prevent infection. Accordingly, the disclosure would need to provide suitable support for this embodiment. However, as previously set forth, the disclosure is not enabling for a protective or therapeutic immune response in patients.

As previously set forth, and contrary to applicants' assertions, sufficient evidence was provided by the Office demonstrating that HIV-1 vaccines are not functional (Haynes, 1993; Graham and Wright, 1995; Haynes, 1996; Lee, 1997). Applicants are directed toward the fifth point of the last Office action wherein it was clearly stated that the prior art is unpredictable and teaches that HIV vaccine attempts have been unsuccessful to date due to a number of caveats including the following: **1) A lack of understanding of the correlates of protective immunity. 2) A lack of understanding of those molecular determinants or antigens governing such responses. 3) The ability of HIV to spread via cell-cell mechanisms. 4) The ability of HIV to reside in immuno-privileged sites such as the CNS. 5) The quasispecies nature of HIV results in immune escape. 6) Inadequate animal models exist for HIV. All of these elements have contributed to vaccine failure.** As Lee (1997) reflects on the status of phase I and II clinical vaccine trials he concludes (left

col., p. 608) that "It is generally recognized that candidate HIV vaccines that have been tested in clinical trials do not elicit long-lasting antibodies or CTL responses." Thus, the prior art clearly teaches that the development of HIV vaccines has been unsuccessful to date.

Applicants' previous suggestion that Examples 7-9 provide sufficient support for the claimed invention is not tenable in view of the prior art discussed *supra* and the other arguments previously raised. The examples referred to involve the administration of an attenuated *Salmonella typhimurium* (designated SL3261) containing either an HIV-1 Tat or RT expression vector to mice. While robust immune responses were obtained following the administration of the attenuated S. *typhimurium* strain, the murine system is not considered an art-recognized model for HIV vaccine development and is not predictive of clinical efficacy. Thus, the results obtained in this study, while promising, cannot be directly extrapolated to the human arena. This is due to a number of obvious genotypic/phenotypic differences between the murine host and humans.

Moreover, applicants' response failed to provide any declaratory or scientific evidence addressing many of the caveats previously raised. For instance, the disclosure fails to provide adequate guidance pertaining to the nature and specificity of those immune responses (i.e., humoral or cell-mediated) that are capable of preventing or inhibiting HIV viral replication. The disclosure fails to provide adequate guidance pertaining to the molecular determinants modulating protective or therapeutic immune responses to HIV. The disclosure also fails to provide any guidance pertaining to the quasispecies nature of HIV-1 and -2. Finally, the disclosure fails to provide any working embodiments demonstrating that a subject has been successfully protected from

viral infection or that any given embodiment of the clinical sequelae associated with HIV infection has been ameliorated. Accordingly, when all the aforementioned factors are considered *in toto*, it would clearly require undue experimentation from the skilled artisan to practice the claimed invention. Therefore, the rejection of the claims is maintained. Applicants may obviate the rejection by directing the claims (as appropriately supported by the specification) towards methods of inducing antibodies in a murine host by administering the attenuated bacterial strain of interest.

35 U.S.C. § 103(a)

6. The following is a quotation of 35 U.S.C. § 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.
>
> Subject matter developed by another person, which qualifies as prior art only under subsection (f) or (g) of section 102 of this title, shall not preclude patentability under this section where the subject matter and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. § 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were

made absent any evidence to the contrary. Applicant is advised of the obligation under 37 C.F.R. § 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. § 103(c) and potential 35 U.S.C. § 102(f) or (g) prior art under 35 U.S.C. § 103(a).

8. Claims 1, 2, 5, and 11 are rejected under 35 U.S.C. § 103(a) as being unpatentable over Brey *et al.* (1992), in view of Georgiou *et al.* (1994), and further in view of Haseltine *et al.* (1991), Kang (1993), and Rodman (1997). As previously set forth, Brey *et al.* (1992) describe the preparation of S. *typhimurium* expression systems (including those derived from strain SL3261) that are useful for the expression of heterologous (e.g., malaria) antigens. This teaching does not disclose the utilization of an Lpp-OmpA-Tat fusion protein. Georgiou *et al.* (1994) describe the preparation of recombinant DNAs that are suitable for the expression of a heterologous antigen on the external surface of an enteric microorganism (e.g., E. *coli* or Salmonella). DNA constructs were prepared that were capable of encoding fusion proteins comprising the Lpp signal sequence, OmpA coding portion, and a heterologous antigen (i.e., see Figure 1). This teaching does not disclose recombinants expressing the HIV-1 *tat* gene. Haseltine *et al.* (1991), Kang (1993), and Rodman (1997) all provide the complete nucleotide/amino acid sequence of the HIV-1 *tat* gene and expression vectors comprising said gene. These teachings all illustrate the medical importance of Tat.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to express the HIV-1 *tat* gene provided by Haseltine *et al.* (1991), Kang (1993), or Rodman (1997), as an Lpp-OmpA-Tat fusion protein,

as suggested by Georgiou *et al.* (1994), in the S. *typhimurium* expression system described by Brey *et al.* (1992), since Brey and colleagues teach that this system is useful for generating strong immune responses against the antigen of interest. The skilled artisan would have been motivated to prepare such constructs since this would facilitate the development of HIV-1 Tat-specific immunological reagents (i.e., antibodies) which can be employed in diagnostic, immunological, or biochemical assays. It would have also been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to prepare a fusion protein comprising the Lpp signal sequence, OmpA, and HIV-1 Tat since Georgiou *et al.* (1994) teach that Lpp-OmpA-X fusion proteins are expressed in large quantities in an antigenic/immunogenic form on the cell surface of enteric bacteria.

9. Claims 1, 2, 5[1], and 11 are rejected under 35 U.S.C. § 103(a) as being obvious over Hone *et al.* (1996) in view of Georgiou *et al.* (1994), and further in view of Haseltine *et al.* (1991), Kang (1993), and Rodman (1997). Hone and colleagues provide attenuated *Salmonella typhimurium* vaccine vectors containing expression vectors encoding *Escherichia coli* OmpA::HIV-1 gp120 fusion proteins. These Salmonella strains induced both mucosal and systemic HIV-1 gp120-specific immune responses. This teaching does

[1] Applicants are further advised that the teachings of Hone and colleagues describes the use of an S. *typhimurium* strain carrying a mutation in the *aro* locus. This attenuated bacterial strain appears to be the same strain described by Fouts *et al.* (1995, Construction and immunogenicity of *Salmonella typhimurium* vaccine vectors that express HIV-1 gp120, Vaccine, 13(17):1697-705) which was designated strain SL3261. Since the Patent Office does not have the facilities for examining and comparing applicants' claimed S. *typhimurium* strain SL3261 with the S. *typhimurium* strain employed by Hone *et al.* (1996), the burden is upon applicants to demonstrate the unobvious genotypic/phenotypic differences between the two strains. *In re Best*, 562 F.2d 1252, 195 U.S.P.Q. 430 (C.C.P.A. 1977). *Ex parte Gray*, 10 U.S.P.Q.2d 1922 (Bd. Pat. Appl. Int. 1989).

not disclose Lpp-OmpA-HIV-1 Tat fusion proteins. Georgiou *et al.* (1994) describe the preparation of recombinant DNAs that are suitable for the expression of a heterologous antigen on the external surface of an enteric microorganism (e.g., E. *coli* or Salmonella). DNA constructs were prepared that were capable of encoding fusion proteins comprising the Lpp signal sequence, OmpA coding portion, and a heterologous antigen (i.e., see Figure 1). This teaching does not disclose recombinants expressing the HIV-1 *tat* gene. Haseltine *et al.* (1991), Kang (1993), and Rodman (1997) all provide the complete nucleotide/amino acid sequence of the HIV-1 *tat* gene and expression vectors comprising said gene. These teachings all illustrate the medical importance of Tat.

Therefore, it would have been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to express the HIV-1 *tat* gene provided by Haseltine *et al.* (1991), Kang (1993), or Rodman (1997), as an Lpp-OmpA-Tat fusion protein, as suggested by Georgiou *et al.* (1994), in the S. *typhimurium* expression system described by Hone *et al.* (1996), since Hone and colleagues teach that this system is useful for generating strong immune responses against the antigen of interest. The skilled artisan would have been motivated to prepare such constructs since this would facilitate the development of HIV-1 Tat-specific immunological reagents (i.e., antibodies) which can be employed in diagnostic, immunological, or biochemical assays. It would have also been *prima facie* obvious to one having ordinary skill in the art at the time the invention was made to prepare a fusion protein comprising the Lpp signal sequence, OmpA, and HIV-1 Tat since Georgiou *et al.* (1994) teach that Lpp-OmpA-X fusion proteins are expressed in large quantities in an antigenic/immunogenic form on the cell surface of enteric bacteria.

Correspondence

10. Correspondence related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Official communications should be directed toward one of the following Group 1600 fax numbers: (703) 308-4242 or (703) 305-3014. Informal communications may be submitted directly to the Examiner through the following fax number: (703) 308-4426. Applicants are encouraged to notify the Examiner prior to the submission of such documents to facilitate their expeditious processing and entry.

11. Any inquiry concerning this communication should be directed to Jeffrey S. Parkin, Ph.D., whose telephone number is (703) 308-2227. The examiner can normally be reached Monday through Thursday from 8:30 AM to 6:00 PM. A message may be left on the examiner's voice mail service. If attempts to reach the examiner are unsuccessful, the examiner's supervisors, James Housel or Laurie Scheiner, can be reached at (703) 308-4027 or (703) 308-1122, respectively. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Respectfully,

Jeffrey S. Parkin, Ph.D.
Patent Examiner
Art Unit 1648

02 December, 2001